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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,217	06/05/2000	EMMANUELLE GUILLOT	1029/00196	1395

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EXAMINER
SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
1634	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/529,217	GUILLOT ET AL.	
	Examiner	Art Unit	
	Jehanne Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Currently, claims 1-30 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is NON-FINAL.

Specification

2. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

The following order or arrangement is preferred in framing the specification and, except for the reference to the drawings, each of the lettered items should appear in upper case, without underling or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.
(b) Cross-Reference to Related Applications.
(c) Statement Regarding Federally Sponsored Research or Development.
(d) Reference to a "Sequence Listing," a table, or a computer program listing appendix submitted on compact disc (see 37 CFR 1.52(e)(5)).
(e) Background of the Invention.
    1. Field of the Invention.

2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) Brief Summary of the Invention.
(g) Brief Description of the Several Views of the Drawing(s).
(h) Detailed Description of the Invention.
(i) Claim or Claims (commencing on a separate sheet).
(j) Abstract of the Disclosure (commencing on a separate sheet).
(k) Drawings.
(l) Sequence Listing, if on paper (see 37 CFR 1.821-1.825).

3. The disclosure and the claims are objected to because of the following informalities: the recitation of SEQ ID N°does not conform to US practice. This objection can be overcome by reciting instead SEQ ID NO: when refering to a sequence descriptor.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps or elements, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are as follows. Claim 1 recites "extracting the hybridized specific probes from their target by adding a denaturing agent to denature the probe target complex...", however the step fails to indicate what the denaturing agent is being added *to*. For

example, the denaturing agent could be added to the solution that contains the microorganisms that contain the probe-target complex, which the specification teaches is the invention and which is indicated in applicants responses, or the denaturing agent could be added to a solution containing only the probe-target complex which was extracted from the whole cells. Applicants responses, however, indicate that the former scenario is the invention, for example, the response of 12/6/2001 states at page 6 (end of last full para), "claim 1 was amended to better define the extraction and separation of the hybridized probes *from the cells* for quantitative detection".

6. Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1 lacks a positive process step relating back to the preamble. The preamble recites a method of qualitative and quantitative analysis of microbial populations but the last step recites detecting extracted probes, thus it is unclear if the method is drawn to analysis of microbial populations or to detecting extracted probes.

B) Claim 17 lacks sufficient antecedent basis for the recitation of said "detecting and amount measurement".

C) Claims 19-23 are indefinite in that it is unclear what the term "it" in line 1 of each claim refers to. If the term is meant to refer to the method, the claim should be amended to reflect such, for example: "the method according to claim 1, wherein said method is used ...".

D) Claim 25 lacks sufficient antecedent basis for the recitation of "said denaturing agent concentration", said Tris HCl concentration" and "said salt concentration". This rejection can be overcome by reciting instead for example" the concentration of said denaturing agent".

E) Claim 25 is indefinite as it is unclear what range of concentrations is encompassed by the terminology of "on the order of". The specification does not define this recitation, and therefore, the metes and bounds of the claim are unclear.

F) Claim 29 lacks sufficient antecedent basis for the recitation of "said fixation solution".

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-6 and 11-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Manz et al (Water Research, vol. 28, pp 1715-1723, 1994), and De Los Reyes et al (Applied and Environmental Microbiology, vol. 63, pp 1107-1117; 1997) in view of Mobarry et al (Applied and Environmental Microbiology, June 1996, vol. 62, pp 2156-2162) and further in view of Walder (US Patent 5,403,711; 4/4/1995) or in the alternative Gordon (WO 97/27328, July 31, 1997).

Manz teaches that cells from activated sludge samples or pure cultures were mechanically disrupted with glass beads and that nucleic acid detection occurred by immobilization of nucleic acids on nylon membranes and probing with digoxigenin-labeled oligonucleotides (p. 1717, col. 1, "total nucleic acid extraction..."). De Los Reyes teaches that oligonucleotide probes were used to quantify abundances of microbial groups in activated sludge and anaerobic digester systems. De Los Reyes teaches that RNA samples were applied to Magna Charge nylon membranes and that the membranes were hybridized with universal and specific probes and that the resulting hybridization responses were used to determine the relative concentration of target SSU rRNA in samples (see p. 1108, col 2, "quantitative membrane hybridization"). De Los Reyes teaches using fluorescence tagged group specific as well as universal probes S-Univ-1390 and Bact-0338 (see p. 1108, col 1). Mobarry et al teach phylogenetic probes for analyzing nitrifying bacteria

(see abstract). Mobarry teaches using probes Nb 1000 and Nso 1225. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that the methods of either Manz or De Los Reyes could be used to detect target nucleic acid sequences from microbial populations using group specific as well as universal labeled probes as De Los Reyes teaches using such to quantify specific microbial populations using methods also taught by Manz. It would have further been prima facie obvious to one ordinary skill in the art that the probes of Mobarry could be used in such a method as Mobarry teaches the detection of microbial samples using probes Nb 1000 and Nso 1225.

Although neither Manz, De Los Reyes, or Mobarry teach extracting the probe from the target, such methods were used at the time of applicant's invention to identify probe target hybridization. For example, Walder et al teach a method of detection of RNA in which a sequence serves as a cofactor for a catalytic reaction in which a complementary, labeled nucleic acid probe is cleaved such that the target sequence is released intact (see abstract). Gordon also teaches the detection of repeat nucleic acid sequences by the number of dissociation events (extracting probe from target) between an oligonucleotide probe and a target nucleic acid (see p. 16, and abstract). Gordon further teaches that a test sample includes cell cultures (see p. 6). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made that labeled probes could be detected hybridized to their target or dissociated therefrom, after hybridization as both Walder and Gorden teach different methods of detecting probe:target hybridization by detecting an unhybridized probe or target. It would have

been prima facie obvious to the ordinary artisan that such methods were equivalent to the methods of Manz or De Los Reyes as Walder and Gorden teach the successful detection of probe:target hybridization. The increase in temperature (thereby increasing stringency of hybridization) taught by Gordon is broadly interpreted to encompass an agent that brings about the denaturation of probe from target. Furthermore, it would have been prima facie obvious to the ordinary artisan that an equivalent method of increasing stringency could be achieved by adding a chemical denaturing agent, such as formaldehyde (or formamide, also known in the art to be a denaturing agent) as De Los Reyes teaches using different concentration of formaldehyde for different hybridization conditions and further teaches that increasing the formaldehyde concentration by 1% was equivalent to increasing the Td by 0.7 degrees Celsius (p. 113, 2nd col. Lines 1-6).

Response to Arguments

The response traverses that there is no teaching in Manz that specific probes come in contact and recognize a mRNA target in whole cells. This argument has been thoroughly reviewed but was found unpersuasive because the instantly pending claims do not specify a positive process step where the probe comes into contact with whole cells or to performing in situ hybridization. As claimed, the instantly rejected claims are drawn to contacting microorganisms with a probe "that recognizes a RNA target sequence under conditions favorable to in situ hybridization in whole cells". The claims do not specify that in situ hybridization is actually performed, nor that actual whole cells are placed in contact with the probe. "Conditions

favorable to in situ hybridization" could simply be a certain temperature or salt concentration that can be used in both the method outlined by Manz or De Los Reyes above and in situ hybridization. The response further traverses that De Los Reyes teaches different concentrations of formaldehyde to fix cells. This argument has been thoroughly reviewed but was found unpersuasive as De Los Reyes teaches using different concentration of formaldehyde for different hybridization conditions and further teaches that increasing the formaldehyde concentration by 1% was equivalent to increasing the Td by 0.7 degrees Celsius.

9. Claims 1-12, 16-18, and 24-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mayrand (US Patent 5,691,146, 102(e) date: 5/5/1995), in view of Burton, Journal of Experimental Marine Biology and Ecology, 1996, vol. 200, abstract, p. 85), and Nuovo et al (US Patent 5,538,871, 7/23/1996) and further in view of De Los Reyes, and Mobarry.

Mayrand teaches that in situ hybridization and amplification can be performed using primers and fluorescently labeled probes (see cols 4 and 5). (see US Patent 5,538,871 for in situ PCR conditions, reference provided). Burton teaches that bacteria can be detected by in situ PCR. De Los Reyes and Mobarry teach universal and specific probes for the detection of microbial populations in waste water. Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the application was made to use the method of Mayrand under in situ PCR conditions for the detection of microbial populations as Burton teaches that in situ PCR can be used to detect bacteria and De Los Reyes and Mobarry teach probes useful for

detecting microbial populations under in situ conditions. The ordinary artisan would have been motivated to use the method of Mayrand, that is to include probes in *in situ* PCR because Mayrand teaches that the method of contacting a target nucleic acid with PCR reagents and specific probes allows a the amplification and detection of target nucleic acid in a single reaction vessel using a single reagent. Although the instantly claimed invention does not specify in situ PCR, the instantly claimed invention is drawn to a method comprising and does not exclude in situ PCR. Further, the method of Mayrand teaches contacting target with PCR reagents and a probe, and during the subsequent thermal cycling steps, the probe of Mayrand will dissociate from the target. Thus the temperature change can be an agent that brings about dissociation or denaturation of the probe from the target. It is noted that Mayrand does not teach elution or detection of the probe outside the cell, however the presently claimed invention is not drawn to such.

Conclusion

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634
September 9, 2002